

# *Helicobacter pylori* seropositivity in subjects with acute myocardial infarction

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## Abstract

**Objective**—To determine whether *Helicobacter pylori* infection increases the risk of myocardial infarction.

**Design**—Case-control study.

**Setting**—University teaching hospital.

**Methods**—Serological evidence of *H pylori* infection was determined in 342 consecutive patients with acute myocardial infarction admitted into the coronary care unit and in 236 population-based controls recruited from visitors to patients on medical and surgical wards.

**Results**—206/342 (60.2%) of cases were *H pylori* positive compared with 132/236 (55.9%) of controls ( $P = 0.30$ ). Age and sex stratified odds ratio for myocardial infarction associated with *H pylori* seropositivity was 1.05 (95% CI 0.7 to 1.53,  $P = 0.87$ ) and this remained non-significant ( $P = 0.46$ ) when other risk factors for ischaemic heart disease were taken into account using logistic regression analysis. *H pylori* seropositivity was not associated with several coronary risk factors in either cases or controls.

**Conclusion**—No increase was found in *H pylori* seropositivity in subjects with acute myocardial infarction. This suggests that previous *H pylori* infection is not a major risk factor for acute myocardial infarction.

236 control subjects for evidence of previous *H pylori* infection.

## Patients and methods

### SUBJECTS

Patients who satisfied the World Health Organisation criteria for MI in terms of symptoms, enzyme increases, or electrocardiographic changes<sup>8</sup> were recruited from admissions to the coronary care unit (CCU) at Leicester Royal Infirmary. The CCU, serving a population of around 300 000, accounts for > 65% of admissions of cases with MI in Leicester. The period of recruitment was between July 1993 and April 1994, and > 97% of eligible subjects were recruited.

Control subjects were recruited from adult visitors to patients with non-cardiovascular illnesses on general medical and surgical wards at the Leicester Royal Infirmary to provide subjects likely to be representative of the source population from which the cases came. A note was made of controls who reported a history of coronary heart disease but such subjects were not excluded. Cases and controls filled in a standard questionnaire about their personal histories, had height and weights measured, and provided blood samples for measurement of serum total and HDL cholesterol and *H pylori* IgG antibodies.

The study was approved by the local clinical research ethics committee.

### BIOCHEMICAL MEASUREMENTS

Serum total and HDL-cholesterol were measured using a Kodak Ektachem E700 CXR Automatic Analyser in a quality-controlled hospital biochemistry laboratory. For cases, the first blood sample taken after admission was used for the analysis.

### DETERMINATION OF *H PYLORI* STATUS

*H pylori* status was established serologically using an established IgG ELISA assay based on an ultracentrifuged sonicate antigen with a sensitivity of 92.3% and a specificity of 90.7%.<sup>9</sup> The sensitivity and specificity values were established using a local Leicester-based dyspepsia population with *H pylori* status being determined by a combination of histology, culture, and urease testing. All samples were assayed in duplicate and samples with borderline values were assessed further by immunoblotting.

### STATISTICAL ANALYSIS

Distribution of *H pylori* seropositivity and

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Among the more intriguing factors to have been linked to the risk of coronary heart disease (CHD) are chronic bacterial infections,<sup>1,2</sup> and recently it has been suggested that *Helicobacter pylori* colonisation from childhood may relate to CHD risk.<sup>3</sup> *H pylori* is now recognised as the major cause of histological chronic gastritis and a necessary factor in the development of duodenal and gastric ulceration. Successful eradication of *H pylori* makes ulcer relapse extremely unlikely.

Until recently, the data supporting a relation between *H pylori* and CHD relied on relatively small case-control studies,<sup>3-5</sup> although two larger conflicting studies<sup>6,7</sup> have just been reported (see Discussion). To investigate further the association between *H pylori* colonisation and CHD we have compared 342 patients with acute myocardial infarction (MI) with

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Table 1 Seropositivity for *Helicobacter pylori* infection in acute myocardial infarction cases and population controls

Group	Cases	Controls
Males	135/229 (59.0%)	81/141 (57.4%)
Females	71/113 (62.8%)	51/95 (53.7%)
Total	206/342 (60.2%)	132/236 (55.9%)

qualitative risk factors between cases and controls or qualitative risk factors between *H. pylori* positive and *H. pylori* negative cases or controls were compared using the chi-squared test. Quantitative sample means were compared by analysis of variance. Odds ratios and 95% confidence intervals (CI) estimating the relative risk of MI associated with *H. pylori* seropositivity were calculated using the Mantel-Haenszel method with stratification for age and sex. Logistic regression was used to analyse the influence of other factors on the odds ratio.

### Results

206/342 (60.2%) of patients and 132/236 (55.9%) of controls were *H. pylori* seropositive (odds ratio 1.19 (95% CI 0.84 to 1.69)  $P = 0.30$ ) (table 1). Controls were significantly younger than patients (56.0 (13.0) (SD) years versus 65.1 (11.7) years,  $P < 0.001$ ). As reported previously,<sup>7</sup> seropositivity increased with age in both our groups (data not shown), making the age-stratified odds ratio even less significant (odds ratio 1.05 (95% CI 0.72 to 1.53),  $P = 0.87$ ).

Table 2 shows the demographic and coronary risk factors in cases and controls grouped by *H. pylori* serological status. All the classic risk factors for CHD were significantly increased ( $P < 0.01$ ) in cases compared with controls. However, there was no difference in either cases or controls when the subjects were classified according to *H. pylori* status (table 2). In logistic regression analysis the association of *H. pylori* positivity with myocardial infarction remained non-significant when adjusted for these risk factors (odds ratio 0.85, 95% CI 0.55 to 1.31,  $P = 0.46$ ).

Leicester has a considerable ethnic community: 11.9% of cases and 6.3% of controls were

non-white. As a whole, *H. pylori* seropositivity was higher in non-white subjects (67.8%) than in white subjects (57.5%) although this did not reach statistical significance ( $P = 0.13$ ). In each group, however, there was no difference in frequency of *H. pylori* infection between cases and controls (59.1% *v* 55.2% for white cases and controls respectively and 68.3% *v* 66.2% for non-white cases and controls). Thus the age and sex stratified odds ratio for white subjects only was 1.05 (95% CI, 0.71 to 1.54,  $P = 0.88$ ). Similarly, the association remained non-significant when only young ( $< 55$  years, median age for controls) cases and controls were compared (odds ratio 1.26, 95% CI 0.66 to 2.41,  $P = 0.45$ ).

### Discussion

There are considerable problems in investigating potential associations between *H. pylori* and CHD.<sup>10</sup> Both conditions are common in the population, both increase with age, and both are associated with socioeconomic status. A causal association between *H. pylori* and CHD if proven is, however, very important in that *H. pylori* is easily screened for and amenable to treatment. There is also the potential for a future vaccine which could be used in childhood, because it is thought that *H. pylori* is predominantly transmitted in childhood.<sup>11</sup>

Previous studies<sup>3-7</sup> examining the relation between *H. pylori* and CHD have used a variety of criteria to define the presence of CHD. Thus in the original report demonstrating an association, subjects with angiographically defined CHD were studied.<sup>3</sup> More recently, in a cross-sectional study of a population based sample of 388 men, the same group found an association when CHD was defined on the basis of either electrocardiographic or symptomatic/historical criteria.<sup>6</sup> Interestingly, the association was strongest when CHD was defined on the basis of ECG changes which included any of the following: Q waves, ST segment depression, left bundle branch block, or T wave inversion. The association with ECG changes remained significant when adjusted for other factors, whereas that with history of angina/MI became non-significant after adjustment. Since several of the ECG

Table 2 Comparison of demographic and coronary risk factors in cases and controls grouped by *Helicobacter pylori* serological status

	Cases			Controls		
	HP+ve	HP-ve	P	HP+ve	HP-ve	P
Age*	65.2 (11.5)	64.8 (12.1)	0.76	57.4 (13.1)	54.4 (12.5)	0.08
Males (%)	65.5	69.1	0.49	61.4	57.7	0.57
White (%)	86.4	90.4	0.26	92.4	95.2	0.39
Current smokers (%)*	31.7	33.6	0.73	20.6	14.4	0.22
Angina (%)*	28.9	27.6	0.83	4.9	9.2	0.22
Hypertension (%)*	33.9	32.0	0.73	19.1	16.3	0.59
Diabetes (%)*	12.2	11.6	0.84	6.9	1.0	0.03
+ve FH (%)*	36.7	41.6	0.45	26.7	22.7	0.44
BMI†	26.2 (4.2)	24.9 (4.1)	0.02	25.7 (3.6)	25.1 (3.6)	0.31
Total cholesterol†	5.5 (1.3)	5.6 (1.1)	0.57	5.7 (1.1)	5.6 (1.1)	0.61
HDL cholesterol†	1.20 (0.36)	1.25 (0.34)	0.31	1.16 (0.29)	1.23 (0.37)	0.15

HP+ve, *H. pylori* seropositive; HP-ve, *H. pylori* seronegative; FH, family history of MI in first degree relative; BMI, body mass index (kg/m<sup>2</sup>).

\* $P < 0.001$  cases *v* controls.

†BMI, total cholesterol and HDL-cholesterol available for 71.6%, 77.5%, 65.5% respectively of cases and 100%, 97.9%, 97.0% of controls. Numbers in parentheses are SD.

changes included could have non-CHD causes, this raises questions about the specificity of the observed association.

In the largest study to date, Murray *et al* recently reported their findings in participants recruited in Northern Ireland as part of the MONICA project.<sup>7</sup> In 2115 subjects between the ages of 25 and 64, *H pylori* seropositivity was 57.6%. 135 subjects (6.4%) had CHD according to the Rose angina questionnaire. After adjustment for age, sex, social class, smoking, and HDL-cholesterol, the odds ratio for CHD for subjects who were *H pylori* seropositive was 1.51 (95% CI, 0.93 to 2.45,  $P = 0.1$ ). The authors concluded that they could not entirely exclude an important association between *H pylori* infection and CHD but that if one did exist it could not account for the social class inequality in CHD.

In the current study only cases who strictly satisfied the WHO criteria for acute MI were recruited. Subjects were recruited prospectively with > 97% recruitment of eligible subjects to provide the largest number of cases so far in whom an association with *H pylori* seropositivity has been examined. Within the confidence intervals of the odds ratios we did not find a significant association between *H pylori* infection and risk of acute MI in either the whole cohort or selected subgroups.

A negative study always raises questions about the power of the study. *A priori* our study had 80% power at a  $P$  value of 0.05 to detect a 1.6-fold increase in risk. As indicated by the 95% confidence intervals obtained for the odds ratios, our study cannot exclude an effect of a lower magnitude of previous *H pylori* infection on MI risk.

A critical feature of any case-control study is the selection of control subjects. They need to provide a reliable estimate of the prevalence of a putative risk factor in the base population from which the cases are recruited. We therefore chose to recruit our controls from individuals visiting patients in the same hospital. Controls were recruited concurrently with the myocardial infarction cases. Using information on the age and sex distribution of myocardial infarction cases admitted to the CCU in the previous year held in our CCU database, we attempted to recruit controls of a mix similar to that of the likely myocardial infarction cases, although no individual willing to participate was excluded. The prevalence of *H pylori* seropositivity in our controls (55.9%) is similar to that observed by Murray *et al*<sup>7</sup> in their cross-sectional study.

Adjustment for several risk factors for CHD did not alter the odds ratio for risk of MI associated with *H pylori* seropositivity. However, a potentially important limitation of our study is lack of information on social class of cases and controls. Prevalence of *H pylori* seropositivity increases from social class I to V.<sup>7,10</sup> Thus despite our efforts to recruit suitable controls (see above), if the cases and controls differed significantly in this variable, it could have masked an association. We cannot exclude this possibility, although it is interesting to note that in their study, Murray *et al*<sup>7</sup> found that

after age and sex were adjusted for, social class did not markedly affect their odds ratio for the association of *H pylori* seropositivity with CHD.

Another possible explanation for our negative finding could be our choice of cases. As mentioned earlier, some previous studies have included not only subjects with MI, but also cases with CHD diagnosed by other criteria. It is possible that *H pylori* infection predisposes primarily to atheroma formation and the association with the downstream phenotype of MI, which has other important contributing factors such as thrombosis, is much weaker. However, against this, we found no increase in prevalence of *H pylori* seropositivity in cases with a previous history of angina (table 2) and the odds ratio with MI remained non-significant when the analysis was restricted to these subjects (data not shown).

Several conventional risk factors were, as expected, more prevalent in our cases compared with controls. However, as reported previously,<sup>6,7</sup> we found no association between *H pylori* serological status and these factors. To explain the relation between *H pylori* and CHD, most attention has focused on acute phase reactants such as fibrinogen, which may be increased in such chronic infections and which in turn may predispose to CHD. Thus, in two separate studies, Patel *et al*<sup>6,12</sup> found higher circulating fibrinogen concentrations in *H pylori* seropositive individuals compared with *H pylori* negative subjects. However, in their much larger cohort, Murray *et al*<sup>7</sup> found no such increase, and, if anything, there was a weak negative association. Therefore, in addition to controversy regarding the existence of a relation between *H pylori* and CHD there is also conflicting data regarding the effect of *H pylori* infection on the favourite intermediary phenotype.

In summary, in a large series of consecutively recruited and unselected acute myocardial infarction cases we were unable to demonstrate any association between *H pylori* colonisation and MI beyond that expected in two conditions which occur commonly in the population and increase with age. This raises serious doubt regarding the association with CHD, and on current evidence one cannot use risk of CHD to justify widespread *H pylori* eradication.

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## STAMPS IN CARDIOLOGY

### Jan Evangelista Purkinje (1787-1869)

Czechoslovakia issued two stamps in 1937 to commemorate the 150th anniversary of the birth of Purkinje (spelt Purkyně in Czech). The label (A) illustrates part of a medical design and features the staff and serpent. It is not incorporated in the stamp (B) and is frequently lost when the stamp is in used condition, the label having been torn off.

Jan Evangelista Purkinje was born in Libochovice, Bohemia, and graduated in medicine from Prague. While he was professor of physiology at the University of Breslau he made several widely acclaimed scientific discoveries. He was one of the very first to use the microscope to explore the function of tissues, "histophysiology" as he called it, and he introduced the term protoplasm. In 1839 he described the subendocardial structures in the

heart, known ever since as the Purkinje fibres. Later it was realised that the network of Purkinje can be seen with the naked eye in the sheep and the ox, and the whole arborisation shown clearly by injecting the sheaths of the fibres with India ink. S Tawara identified the atrioventricular node in 1906 and showed that the AV bundle was prolonged into the Purkinje network. A few years later it was possible with Einthoven's invention of the electrocardiograph to quantify the rate of conduction and rhythmicity in the Purkinje substance. Purkinje has ten other eponymous descriptions to his name, the best known being the cells in the cerebellum. He described the classification of fingerprints and their importance for identification.

M K DAVIES  
A HOLLMAN



(A)



(B)